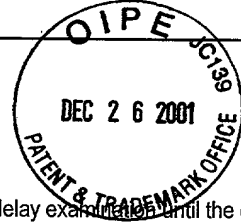


FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		ATTORNEY'S DOCKET NUMBER: BE 4035 U.S. APPL. NO. (If known, see 37 CFR 1.5) 10/019000
INTERNATIONAL APPLICATION NO.: PCT/FR00/01712	INTERNATIONAL FILING DATE: 21 JUNE 2000 (21.06.00)	PRIORITY DATE CLAIMED: 22 JUNE 2000 (22.06.99)
TITLE OF INVENTION: PROCESS FOR THE ANALYSIS OF A SAMPLE OF A COMPLEX MOLECULE RELATIVE TO A REFERENCE BATCH OF THE SAME COMPLEX MODULE		
APPLICANT(S) FOR DO/EO/US: Gérard MARTIN and Gilles MARTIN		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
1. <input checked="" type="checkbox"/> 2. <input type="checkbox"/> 3. <input checked="" type="checkbox"/> 4. <input checked="" type="checkbox"/> 5. <input checked="" type="checkbox"/> a. <input checked="" type="checkbox"/> b. <input type="checkbox"/> c. <input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/> 10. <input type="checkbox"/> 11. <input checked="" type="checkbox"/> 12. <input type="checkbox"/> 13. <input checked="" type="checkbox"/> <input type="checkbox"/> 14. <input type="checkbox"/> 15. <input type="checkbox"/> 16. <input checked="" type="checkbox"/>	This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1). A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date. A copy of the International Application as filed (35 U.S.C. 371(c)(2)) a. <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau <u>--in French language</u>). b. <input type="checkbox"/> has been transmitted by the International Bureau. (see attached copy of PCT/IB/308) c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). A translation of the International Application into English (35 U.S.C. 371(c)(2)). Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)). a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> have been transmitted by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input type="checkbox"/> have not been made and will not be made. A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). A translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). Item 11. to 16. below concern document(s) or information included: An Information Disclosure Statement under 37 CFR 1.97 and 1.98. An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. A FIRST preliminary amendment. A SECOND or SUBSEQUENT preliminary amendment. A substitute specification. A change of power of attorney and/or address letter. Other items or information: INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT/IPEA/409--in French language), INTERNATIONAL SEARCH REPORT (PCT/ISA/210), APPLICATION DATA SHEET, ABSTRACT	



U.S. APPLICATION NO. (if known, see 37 CFR 1.51) <div style="font-size: 24pt; font-weight: bold; text-align: center;">10/019000</div>		INTERNATIONAL APPLICATION NO. PCT/FR00/01712		ATTORNEY'S DOCKET NO. BE 4035	
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<div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;"> 17. <input checked="" type="checkbox"/> The following fees are submitted: </div> <p>BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$ 1,040.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$ 890.00</p> <p>International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$ 740.00</p> <p>International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$ 710.00</p> <p>International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$ 100.00</p>	CALCULATIONS PTO USE ONLY
--	----------------------------------

ENTER APPROPRIATE BASIC FEE AMOUNT =				\$	890.00
Surcharge of \$130.00 for furnishing the oath or declaration later than 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	130.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$	
Total claims	3 - 20 =	0	X \$18.00	\$	
Independent claims	1 - 3 =	0	X \$84.00	\$	
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)			+ \$280.00	\$	
TOTAL OF ABOVE CALCULATIONS =				\$	1020.00

Reduction of 1/2 for filing by small entity, if applicable. Applicant claims Small Entity Status under 37 CFR 1.27.				\$	
SUBTOTAL =				\$	1020.00

Processing fee of \$130 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492(f)).				\$	
TOTAL NATIONAL FEE =				\$	1020.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				\$	
TOTAL FEES ENCLOSED =				\$	1020.00

	Amount to be refunded:	
	charged:	

a.	<input checked="" type="checkbox"/>	A check in the amount of \$ 1020.00 to cover the above fees is enclosed.
b.	<input type="checkbox"/>	Please charge my Deposit Account No. 25-0120 in the amount of \$ to cover the above fees. A duplicate copy of this sheet is enclosed.
c.	<input checked="" type="checkbox"/>	The Commissioner is hereby authorized to charge any additional fees which may be required by 37 CFR 1.16 and 1.17, or credit any overpayment to Deposit Account No. 25-0120 . A duplicate copy of this sheet is enclosed.

SEND ALL CORRESPONDENCE TO:

YOUNG & THOMPSON
 745 South 23rd Street
 2nd Floor
 Arlington, VA 22202
 (703) 521-2297
 facsimile (703) 685-0573
Customer Number: 000466

December 26, 2001

By **Thomas W. Perkins**
 Attorney for Applicant
 Registration No. 33,027

10/019000

531 Rec'd PCT

26 DEC 2001

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Gérard MARTIN et al.

Box Non-fee Amendment

Serial No. (unknown)

GROUP

Filed herewith

Examiner

PROCESS FOR THE ANALYSIS OF A SAMPLE OF
A COMPLEX MOLECULE RELATIVE TO A REFERENCE
BATCH OF THE SAMPLE COMPLEX MODULE

PRELIMINARY AMENDMENT

Commissioner for Patents

Washington, D.C. 20231

Sir:

Prior to the first Official Action and calculation
of the filing fee, please amend the above-identified applica-
tion as follows:

IN THE CLAIMS:

Please amend claim 3 as follows:

--3. (Amended) Process according to claim 1,

characterized in that, during production of the complex
reference molecule before being subjected to the same cleavage
reactions as the complex molecule to be analyzed, there is
selected at least one primary material and/or an intermediate
product and/or material synthesis conditions to give to at
least one of the cleavage products of the reference complex
molecule a unique characteristic detectable during analysis
without enrichment by isotopic marking and/or the addition of
exogenous elements.--

10019000-043203

Gérard MARTIN et al.

IN THE ABSTRACT:

Please delete the abstract as originally filed which appears on the cover sheet of the Published Application. Add new abstract as enclosed herewith on a separate sheet.

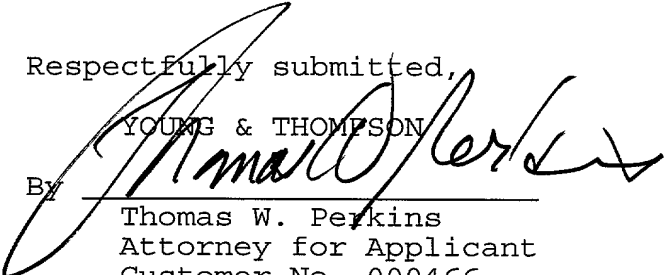
REMARKS

Claim 3 has been amended to correct multiple dependency. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE".

Respectfully submitted,

YOUNG & THOMPSON

By


Thomas W. Perkins
Attorney for Applicant
Customer No. 000466
Registration No. 33,027
745 South 23rd Street
Arlington, VA 22202
703/ 521-2297

December 26, 2001

10019000 042202

"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

Claim 3 has been amended as follows:

3. (Amended) Process according to ~~one of claims 1 and 2~~
claim 1,

characterized in that, during production of the complex reference molecule before being subjected to the same cleavage reactions as the complex molecule to be analyzed, there is selected at least one primary material and/or an intermediate product and/or material synthesis conditions to give to at least one of the cleavage products of the reference complex molecule a unique characteristic detectable during analysis without enrichment by isotopic marking and/or the addition of exogenous elements.

ABSTRACT

The invention concerns a method for analyzing a sample of a complex molecule relatively to a reference batch of the same complex molecule. Said method is characterized in that it consists in breaking up the complex molecule into at least two molecular sub-entities; in determining, on the basis of the atomic sites of said products of the breakup involved in the breakup reactions, the isotope(s) to be analyzed; and in establishing, for at least part of the breakup products, their isotopic profile; and in comparing the isotopic profile of the products of the breakup with the isotopic profile of the raw material(s) previously indexed and/or with the isotopic profile of the reference complex molecule subjected to the same breakup reactions. The invention is useful for detecting counterfeiting in manufacturing processes.

10015000-042202

PTO/PCT Rec'd 22 APR 2002

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Gérard MARTIN et al.

CONFIRMATION NO. 8044

Serial No. 10/019,000
(PCT/FR00/01712)

BOX PCT

Filed December 26, 2001

PROCESS FOR ANALYSIS OF A SAMPLE
OF A COMPLEX MOLECULE RELATIVE
TO A REFERENCE BATCH OF THE
SAME COMPLEX

SUPPLEMENTAL PRELIMINARY AMENDMENT

Commissioner for Patents

Washington, D.C. 20231

Sir:

Prior to the issuance of an action on the merits,
please amend the above-identified application as follows:

IN THE SPECIFICATION:

Replace the paragraph beginning at page 15, line 22,
with the following rewritten paragraph:

--The isotopic ratios $R(i)$ are expressed in deviations
 $\delta(i)$ 0/00 relative to an international reference $R(\text{ref})$ by means
of the relationship:

$$\delta(i) = ((R(i)/R(\text{ref}))-1)*1000$$

^2H and ^{18}O : V. SMOW (Vienna-Standard Mean Ocean Water)

^{13}C : V.PDB (Vienna-Pee Dee Belemnite)

^{15}N : atmospheric nitrogen

10019000-042201

³⁴S: CDT, specimen of Troilite extracted from Diablo Canyon (USA)--

Replace the paragraph beginning at page 16, line 7, with the following rewritten paragraph:

--The benzene rings of fossil origin (petroleum) are characterized by values of $\delta^2\text{H}$ comprised between -20 and -120 0/00 and the saturated side chains between 0 and -70. Measurements are carried out by NMR (SNIF-NMR) for the side chains and the overall content by Mass Spectrometry (MSIR). The overall contents in ^{13}C measured by MSIR are generally equal to -28.5 0/00 with a typical variation of the order of 2 0/00 and the isotopic contents of ^{13}C of the alkylated or functional side chains are measured by NMR. According to the synthesis process and the origin of the primary material of the side chains, the values $\delta^{13}\text{C}$ can vary between -5 and -100 0/00 and thus offer an important characterization potential.--

Replace the paragraph beginning at page 16, line 20, with the following rewritten paragraph:

--Nitrated molecules of synthetic origin have ^{13}C and ^{15}N values, measured by MSIR, which are relatively low and equal respectively to -30 0/00 (1.5) and -20 0/00 (10) but, in this latter case, the cyclization reactions of pyrazoles and xanthenes lead to substantial impoverishment in heavy isotopes. At this level, it can be considered that the values of $\delta^{15}\text{N}$ of the CN group or of the CONH_2 group reflect those of the primary

materials because the introduction into the 1H-pyrazole pattern takes place without significant isotopic fractionation. The content in ^{15}N of the NH_2 group is all the lower relative to that of the primary material, the lower is the yield of the reaction.--

Replace the paragraph beginning at page 17, line 15, with the following rewritten paragraph:

--Finally, it is interesting to note that the isotopic mapping of citric acid is very well defined and that the origin of the sildenafil citrate can be precisely determined by consideration of the isotopic distribution in the citrate fragment. Thus, the content of ^2H measured by NMR varies between -40 and -80 0/00 for biotechnological citric acids but the values $\delta^{13}\text{C}$ are equal respectively to -11 0/00 (1) or -25 0/00 (1) accordingly as the primary material is constituted by a C34 or C3 sugar. The natural citric acids extracted from fruits such as citrus, pineapple or red fruits have $\delta^2\text{H}$ values that are very near to 0 0/00 (25).--

Replace the paragraph beginning at page 18, line 9, with the following rewritten paragraph:

--d) Characterization of the different reaction steps by establishment of an isotopic fractionation profile:

▪ Step: level -4 --→ level -3

No modification of the ^2H and ^{13}C contents of the benzene ring is achieved and, in the same way, the $\delta^{18}\text{O}$ value of the ethoxy group

must not vary. The most significant variation is in the NH_2 function of P(-4a) which is subject to isotopic fractionation $^{15}\text{N}/^{14}\text{N}$ proportional to the kinetic effect α of the formation reaction of the amide bond and the corresponding fractionation is measured by MSIR.--

Replace the paragraph beginning at page 18, line 23, with the following rewritten paragraph:

--The $\text{O}-\text{C}_2\text{H}_5$ group is naturally marked with ^2H , ^{13}C or ^{18}O from suitably chosen ethanol molecules. An ethanol synthesis has ^2H values equal respectively to -100 and -160 0/00 at the two CH_3 and CH_2 sites with ^{13}C contents of the order of -28 to -31 0/00 and ^{18}O contents equal to -5-10 0/00. Moreover, a natural ethanol could have ^2H , ^{13}C , or ^{18}O contents equal respectively to -200 and -400 0/00 (^2H), -11 0/00 (^{13}C) and +7/+10 (^{18}O). These two types of commercially available ethoxy groups without enriched addition, are easily introduced into the o-hydroxybenzoic acid molecule by means of conventional reactions to form the primary material P(-4b). The isotopic characteristics of this primary material, which become a typical fragment as described above, are present in the final molecule of sildenafil citrate.--

IN THE CLAIMS:

Amend claim 1 as follows:

1. (amended) Process for the analysis of a sample of a

complex molecule relative to a reference batch of the same complex molecule so as to determine their degree of similarity and/or the nature of their process of production,

characterized in that the complex molecule is cleaved into at least two molecular sub-entities, in that, if necessary, this cleavage being repeatable on the molecular sub-entities until analyzable and isolable molecular sub-entities are obtained, in that there is determined, as a function of the atomic sites of the cleavage products in question, by generally chemical cleavage reactions, the isotope or isotopes to be studied, in that there is established, for at least a portion of the cleavage products, their isotopic profile and in that the isotopic profile of the cleavage products is compared to the isotopic profile of primary materials already cataloged and taking part in the synthesis process of the reference complex molecule and/or in the isotopic profile of the cleavage products of the reference complex molecule subjected to the same cleavage reactions.

REMARKS

The accompanying changes to the specification and claim merely place this national stage application in the same condition it was during chapter II of the international stage. The undersigned registered patent attorney hereby states that no new matter has been added.

Attached hereto is a marked-up version of the changes made to the specification and claim 1. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

YOUNG & THOMPSON

By



Benoît Castel
Attorney for Applicants
Registration No. 35,041
745 South 23rd Street
Arlington, VA 22202
Telephone: 521-2297

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph beginning at line 22 of page 15 has been amended as follows:

The isotopic ratios $R(i)$ are expressed in deviations $\delta(i)$ [□] 0/00 relative to an international reference $R(ref)$ by means of the relationship:

$$\delta(i) = ((R(i)/R(ref)) - 1) * 1000$$

2H and ^{18}O : V. SMOW (Vienna-Standard Mean Ocean Water)

^{13}C : V.PDB (Vienna-Pee Dee Belemnite)

^{15}N : atmospheric nitrogen

^{34}S : CDT, specimen of Troilite extracted from Diablo Canyon (USA)

Paragraph beginning at line 7 of page 16 has been amended as follows:

The benzene rings of fossil origin (petroleum) are characterized by values of $\delta ^2H$ comprised between -20 and -120 [□] 0/00 and the saturated side chains between 0 and -70. Measurements are carried out by NMR (SNIF-NMR) for the side chains and the overall content by Mass Spectrometry (MSIR). The overall contents in ^{13}C measured by MSIR are generally equal to -28.5 [□] 0/00 with a typical variation of the order of 2 [□] 0/00 and the isotopic contents of ^{13}C of the alkylated or functional side chains are measured by NMR. According to the synthesis process and the origin of the primary material of the side chains, the values $\delta ^{13}C$ can vary between [""5] -5 and -100 [□]

0/00 and thus offer an important characterization potential.

Paragraph beginning at line 20 of page 16 has been amended as follows:

Nitrated molecules of synthetic origin have ^{13}C and ^{15}N values, measured by MSIR, which are relatively low and equal respectively to -30 [□] 0/00 (1.5) and -20 [□] 0/00 (10) but, in this latter case, the cyclization reactions of pyrazoles and xanthenes lead to substantial impoverishment in heavy isotopes. At this level, it can be considered that the values of $\delta^{15}\text{N}$ of the CN group or of the CONH_2 group reflect those of the primary materials because the introduction into the 1H-pyrazole pattern takes place without significant isotopic fractionation. The content in ^{15}N of the NH_2 group is all the lower relative to that of the primary material, the lower is the yield of the reaction.

Paragraph beginning at line 15 of page 17 has been amended as follows:

Finally, it is interesting to note that the isotopic mapping of citric acid is very well defined and that the origin of the sildenafil citrate can be precisely determined by consideration of the isotopic distribution in the citrate fragment. Thus, the content of ^2H measured by NMR varies between -40 and -80 [□] 0/00 for biotechnological citric acids but the values $\delta^{13}\text{C}$ are equal respectively to -11 [□] 0/00 (1) or -25 [□] 0/00 (1) accordingly as the primary material is constituted by a C34 or C3 sugar. The natural citric acids extracted from fruits

such as citrus, pineapple or red fruits have $\delta^2\text{H}$ values that are very near to 0 [□] 0/00 (25).

Paragraph beginning at line 9 of page 18 has been amended as follows:

d) Characterization of the different reaction steps by establishment of an isotopic fractionation profile:

▪ Step: level -4 --> level [3] -3

No modification of the ^2H and ^{13}C contents of the benzene ring is achieved and, in the same way, the $\delta^{18}\text{O}$ value of the ethoxy group must not vary. The most significant variation is in the NH_2 function of P(-4a) which is subject to isotopic fractionation $^{15}\text{N}/^{14}\text{N}$ proportional to the kinetic effect α of the formation reaction of the amide bond and the corresponding fractionation is measured by MSIR.

Paragraph beginning at line 23 of page 18 has been amended as follows:

The $\text{O}-\text{C}_2\text{H}_5$ group is naturally marked with ^2H , ^{13}C or ^{18}O from suitably chosen ethanol molecules. An ethanol synthesis has ^2H values equal respectively to [100] -100 and [160 □] -160 0/00 at the two CH_3 and CH_2 sites with ^{13}C contents of the order of [28] -28 to [31 □] -31 0/00 and ^{18}O contents equal to [-5-10 □] -5-10 0/00. Moreover, a natural ethanol could have ^2H , ^{13}C , or ^{18}O contents equal respectively to [200] -200 and [400 □] -400 0/00 (^2H), -11 [□] 0/00 (^{13}C) and +7/+10 (^{18}O). These two types of commercially available ethoxy groups without enriched addition,

are easily introduced into the o-hydroxybenzoic acid molecule by means of conventional reactions to form the primary material P(-4b). The isotopic characteristics of this primary material, which become a typical fragment as described above, are present in the final molecule of sildenafil citrate.

IN THE CLAIMS:

Claim 1 has been amended as follows:

1. (amended) Process for the analysis of a sample of a complex molecule relative to a reference batch of the same complex molecule so as [particularly] to determine their degree of similarity and/or the nature of their process of production, characterized in that the complex molecule is cleaved into at least two molecular sub-entities, in that, if necessary, [at least one of the cleavage products is cleaved into at least two new molecular sub-entities and in that] this cleavage [operation is repeated on at least a portion of the cleavage products] being repeatable on the molecular sub-entities until analyzable and isolable molecular sub-entities are obtained, in that there is determined, as a function of the atomic sites of the cleavage products in question, by generally chemical cleavage reactions, the isotope or isotopes to be studied, in that there is established, for at least a portion of the cleavage products, their isotopic profile and in that the isotopic profile of the cleavage products is compared to the isotopic profile of primary

MARTIN et al. S.N. 10/019,000

materials already cataloged and taking part in the synthesis process of the reference complex molecule and/or in the isotopic profile of the cleavage products of the reference complex molecule subjected to the same cleavage reactions.

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10/019000

531 Rec'd PC 26 DEC 2001

PROCESS FOR THE ANALYSIS OF A SAMPLE OF A COMPLEX MOLECULE
RELATIVE TO A REFERENCE BATCH OF THE SAME COMPLEX MOLECULE

The present invention relates to a process for the
analysis of a sample of a complex molecule relative to a
5 reference batch of the same complex molecule, so as
particularly to determine their degree of similarity and/or
the characterization of their process of production.

Counterfeiting complex products has become a veritable
scourge, in particular in the fine chemical, cosmetic and
10 pharmaceutical industries. The detection of counterfeiting
of complex products by physico-chemical analysis is often
based on the analysis of traces of secondary products of
the synthesis, of catalysts or impurities. For example, it
has been determined by chromatographic analysis in liquid
15 phase (Asakawa, Shuichi; Kato, Koichi; Inoma,
SusumuHakodate Customs Laboratory, Hakodate-shi, 040,
Japan, Kanzei Chuo Bunsekishoho (1997), 36, 37-43) that
certain glyphosphate base herbicides, produced in the
United States and imported into Japan, infringe Japanese
20 patents. By also using a gas phase chromatographic
technique coupled with mass spectrometry, E. Charton, M.
Wierer, J.M. Spieser, A. Van Dorsselaer, and G. Rautmann
(European Department for the Quality of Medicines, Council
of Europe, Strasbourg, F-67029, Pharm. Pharmacol. Commun.

10015000-043002

100-19000-042202

(1999), 5(1), 61-66) have been able to detect a counterfeit of a medication, somatropine, described in the European pharmacopea, which was in fact a product derived from somatropine of human origin. Conventional chemical methods

5 have permitted proving that tablets of a narcotic substance, fenethylline, were prepared by copying a German patent (N. Al-Gharably and A.R. Al-Obaid, College of Pharmacy, Kind Saud University, Riyadh, 11451, Saudi Arabia, J. Forensic Sci. Soc. (1994), 34(3), 165-7).

10 Similarly, counterfeiting of antibiotics of the β -lactam series have been studied by capillary electrophoresis, at the "National Forensic Chemistry Center" of the "U.S. Food and Drug Administration", 1141 Central Parkway, Cincinnati, OH, 45202, USA and described in the Journal of

15 Chromatography, A (1994), 674(1-2), 153-63.

These compositional methods are not always effective and they can lead to false positives. Moreover, they cannot be used in all cases because of the absence of characteristic tracers.

20 Another process for the authentication of the origin of a product constituted by a mixture of organic compounds, is described in French patent 2.673.291. This process comprises a separative analysis step for the product by gas phase chromatography, a step of transformation to CO₂ by

10019000-042202

combustion of the compounds of the product, followed by a step of analysis by isotopic mass spectrometry so as to measure the enrichment in C_{13} of each compound of the mixture before choosing a compound to mark, particularly by
5 modifying the enrichment in C_{13} of this compound or by adding similar molecules whose richness in C_{13} has first been increased or decreased. Enrichment by isotopic marking necessary for the authentication of the origin of a product is a major drawback of this process. Thus, this
10 step requires the manufacturer to modify his industrial process to be able to mark and authenticate his products. This requirement is connected to the series of steps used in the analysis process, these steps being unable to obtain sufficiently detailed information as to the origin of the
15 products to avoid a marking step of the product by enrichment.

There is also known, as is described in British Patent 2120007, an analysis process consisting in fragmenting a molecule by means of an electron beam in a mass
20 spectrometer chamber with double focusing to obtain metastable ions analyzable by means of said mass spectrometer. However, in this process, the step of fragmentation does not permit obtaining molecular sub-entities, products perfectly stable and isolable, but

rather metastable ions of a lifetime of the order of several fractions of a second. Moreover, the nature of the fragments as well as the molecular site where the cleavage is carried out by the electron beam of the mass spectrometer, are conditioned by the presence of the isotope to be determined. These two characteristics of this process distinguish it fundamentally from a process in which a mass spectrometer is used for the isotopic ratios.

Correspondingly, more powerful analytic techniques have been developed. Such is the case of the mass spectrometry of isotopic ratios (MSIR). Thus, it is possible to characterize the natural specific isotopic fractionation by Nuclear Magnetic Resonance (NMR-FINS method) by measuring the isotopic contents at several molecular sites (or even all the sites) of a molecule. However, this technique is at present used only for simple molecules that can be directly analyzed.

An object of the present invention is to provide a process for the analysis of complex molecules based on an original methodology using isotopic techniques in natural abundance.

Another object of the present invention is to provide a process for the analysis of complex molecules permitting differentiating a batch of complex molecules relative to

another batch and establishing a posteriori the history of the process of production of such a complex molecule without having first modified the process for production of such a complex molecule.

5 To this end, the invention has for its object a process for the analysis of a sample of a complex molecule relative to a reference batch of the same complex molecule so as particularly to determine their degree of similarity and/or the characterization of their process of production, characterized in that the complex molecule is cleaved into at least two molecular sub-entities, in that, if necessary, at least one of the cleavage products is cleaved into at least two new molecular sub-entities and in that this cleavage operation is repeated on at least a portion of the cleavage products until there are obtained analyzable and isolable molecular sub-entities, and in that there is determined, as a function of the atomic sites of the cleavage products in question, by generally chemical cleavage reactions, the isotope or isotopes to be studied, in that there is established, for at least one portion of the cleavage products, their isotopic profile and in that the isotopic profile of the cleavage products is compared to the isotopic profile of the first materials already cataloged and taking part in the synthesis process of the

reference complex molecule and/or in the isotopic profile of the cleavage products of the reference complex molecule subjected to the same cleavage reactions.

5 The performance of the above steps permits applying such a process to no matter what complex molecule, without having proceeded to marking, particularly by enrichment in isotopes of the complex molecule to be analyzed.

10 According to a particular embodiment of the invention, starting with a selected isotope or isotopes, there is established the isotopic profile of at least a portion of the cleavage products at least by nuclear magnetic resonance (NMR) for measurement of the specific positional isotopic content and if desired by mass spectrometry of the isotopic ratios (MSIR) for the measurement of the overall
15 isotopic content. It is to be noted that in the two preceding paragraphs, and in what follows, there is meant by isotopic profile the determination of the isotopic abundance at one or several sites of a molecule and not the measurement of the overall isotopic ratio of the whole
20 molecule, which ratio is measured by isotopic mass spectrometry.

The invention resides in the following discovery by the inventors. Most of the organic molecules are obtained by means of a reaction sequence comprising a number of

steps which can often be large when the complexity of the molecule increases. Each of these steps is characterized by kinetic isotopic effects (and/or thermodynamic effects) which give rise to specific isotopic fractionation, which is to say a selective isotopic marking, at the atomic sites (H, C, N, O...) directly implicated in the reaction or located in the immediate vicinity of the reaction sites. It is thus possible to establish a chart of isotopic distribution of a complex molecule from isotopic profiles of the different steps used. The influence of the first materials and of the intermediate reagents adapted to be used, is also taken into account for establishing the isotopic profile of the molecule based on the individual profiles of a more or less great number of its constituent fragments.

Authentication takes place as follows:

On a sample of authentic product P_0 constituting the reference complex molecule, there is carried out a selective cleavage reaction of the molecule into at least two molecular sub-entities P_{-1a} and P_{-1b} that are lighter. The isotopic effects associated with this cleavage reaction are determined. The specific isotopic compositions of P_{-1a} and P_{-1b} are thus unequivocally connected to that of P_0 . The specific isotopic parameters of the molecular sites of the

fragments are measured by the SNIF-NMR method (^2H , ^{13}C , ^{15}N). A measurement of the overall isotopic content by isotopic mass spectrometry (MSIR) can also be carried out (^{13}C , ^2H , ^{18}O , ^{15}N , ^{34}S). The selection of the isotopes to be analyzed is done on the basis of reference data and spectroscopic characteristics of the fragment. In numerous cases, the SNIF- NMR measurement of ^2H will suffice for the characterization.

. if the P_{-1} fragments have a molecular size incompatible with a direct study by SNIF-NMR, the analysis sequence is restarted from $\text{P}_{-1}(\text{a or b})$ to $\text{P}_{-2}(\text{a or b})$ and so on until molecules generally used as primary or intermediate materials are obtained for the synthesis in organic industry.

The same study is then carried out, strictly under the same experimental conditions, on the complex molecule to be analyzed constituted for example by a product suspected of being a counterfeit or the result of an illicit patent copying. The comparison of the results obtained in the two studies permits establishing an irrefutable conclusion as to the conformity or non-conformity of the product and of the process used. These two steps on the basis of the process suffice to answer the question: conforming or non-conforming?

Setting aside the isotopic reaction effects, the isotopic parameters of the fragments Pi determined from the above authentication process are representative of relatively simple molecules which are frequently intermediates of the industrial synthesis of the medication or of the active product in question. These parameters therefore constitute reliable indicators of the basic elements used by the producing company and can be the object of a more rigorous investigation. In the case of non-conformity, they permit, with reference to the data on the molecules of modest size which may already be cataloged, characterizing the origin of the primary materials of the counterfeit product. One can thus conclude, not only that the product does not conform but that it has been prepared by such a catalog process or from such cataloged primary material. The analysis process described above thus permits if desired identifying the process used in the production of a non-authentic complex molecule.

Moreover, the producer who desires ultimately to authenticate his medication or active product, even if not protected by a patent, can introduce into his production system one or several synthetic intermediates, corresponding to one or several Pi fragments having an

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isotopic profile peculiar to themselves. This method creates in effect a marking of the product without the need to add an oxogenous marking element (as is the case during use of particular compound markers, metal traces, or products enriched in heavy isotopes such as ^{13}C). A specific isotopic footprint can thus be conferred on the synthesis intermediate (molecule of medium size itself synthesized from petroleum derivatives or extracted from vegetable materials, etc.), either by selecting initial primary materials of a particular and constant isotopic content, or by acting on the isotopic effects associated with the reactions of preparation, extraction, purification of the intermediate corresponding to Pi. In the presence of kinetic isotopic effects, a variation of the yield for example can suffice to modify the fractionation and hence the isotopic profile of the synthetic intermediate. By applying the above analysis process to the complex molecule thus elaborated, there will be obtained one or more Pi fragments on which a unique isotopic profile has been conferred. The company will thus have isotopic parameters of one or several fragments of its product which will be unique to it. With this strategy, the product will not suffer the drawbacks which attach to the addition of exogenous elements or to the enrichment by isotopic

marking. During inspection, the suspect product is studied under the conditions described above and the interpretation is carried out in the same way by comparison of the parameters of the fragments of the suspect product and of the reference product. In this case, the control can be simplified because it suffices to characterize the typical fragment or fragments. With this process, the producer has a practically incontestable method of characterizing his product and even of characterizing the batches of it because he need only change the source of a primary material or the conditions of synthesis of a fragment, to give to Pi a typical profile.

In short, in the scope of the analysis process described above, it is possible, during production of the complex reference molecule which can be subjected to the same cleavage reactions as the complex molecule to be analyzed, to select at least one primary material and/or intermediate product and/or conditions of synthesis, so as to give to at least one of the cleavage products of the reference complex molecule, called Pi, as above a unique character detectable during analysis without enrichment by isotopic markers and/or the addition of exogenous materials.

It is to be noted that the fragments or molecular sub-
units are obtained by suitable chemical degradation
processes such as are described in the example of use. The
fragments are then separated and purified by various
5 techniques, as for example liquid phase chromatography,
gaseous phase chromatography or chromatography on silica
gel, distillation, recrystallization, etc. The extraction
purification protocols are first carefully standardized to
avoid any uncontrolled isotopic fractionation.

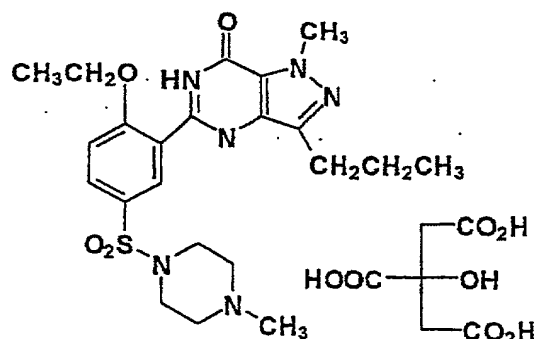
10 An example of analysis of the process of production of
a complex molecule is described below.

a) Description of the molecule to be analyzed:

By way of illustration of the process, let us consider
the case of sildenafil citrate [VIAGRA, trademark] produced
15 by Pfizer, belonging to the category of anti-anginal agents
of the pyrazolopyrimidinone type.

Sildenafil citrate has the following chemical
structure:

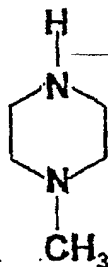
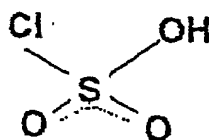
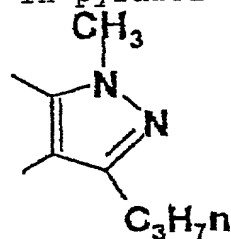
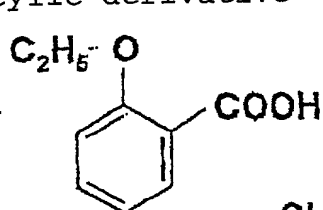
C₂₂ H₃₀ N₆ O₄ S, citrate M = 474.6



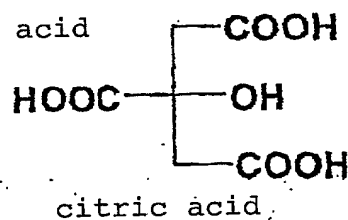
1-[4-éthoxy-3-(6,7-dihydro-1-méthyl-7-oxo-3-propyl-1 H-pyrazolo[4,3-d]pyrimidin-5-yl)pnénylsulphonyl]-4-méthylpiperazine citrate

This molecule can be cleaved into several molecular fragments bearing a characteristic isotopic message, called "isotopic synthons"

Salicylic derivative Substituted 1H-pyrazole



Chlorosulphonic acid



methylpiperazine

citric acid

[illegible]

Occurrence and synthesis methods that can be used for primary materials P-1b, P-2b, P-4a1, P-4a2 and P-4b:

P-1b: N-methylpiperazine $C_5H_{12}N_2$ M = 100.16 CAS 109-01-3

P-2b: chloro-sulfonic acid SO_3HCl M = 116.52 CAS 7790-94-5

5 P-4a1 and P-4a2: 1H-pyrazole, 1-methyl, 3-n propyl, 4-amino, 5-cyano or acetamido

$C_8H_{12}N_4$ or $C_8H_{14}N_4O$

10 The synthesis of the substituted 1H-pyrazole ring can take place by means of a cyclization reaction in hydrazone from ethyl acylacetate and nucleophilic addition of the CN ion to the carbonyl of the cyclic hydrazone.

P-4b: 2-ethoxy

benzoic acid $C_9H_{10}O_3$ M = 166.18 CAS 134-11-2

15 The primary materials P-1b, P-2b and P-4b are available commercially but it is interesting to prepare P-4a1 and P-4a2 by means of conventional syntheses of the 1H-pyrazole rings. These syntheses generally use substituted hydrazines of the R_1NH-NH_2 type and α -dicarboxyl compounds $R_3-CO-CH_2-CO-R_4$.

20 The isotopic contents of the usable primary materials are well documented in the literature.

The isotopic ratios $R(i)$ are expressed in deviations $\delta(i)$ \square relative to an international reference $R(ref)$ by means of the relationship:

$$\delta (i) = ((R(i)/R(\text{ref}))-1)*1000$$

²H and ¹⁸O: V. SMOW (Vienna-Standard Mean Ocean Water)

¹³C: V.PDB (Vienna-Pee Dee Belemnite)

¹⁵N: atmospheric nitrogen

5 ³⁴S: CDT, specimen of Troilite extracted from Diablo Canyon
(USA)

The benzene rings of fossil origin (petroleum) are characterized by values of δ ²H comprised between -20 and -120 ‰ and the saturated side chains between 0 and -70.

10 Measurements are carried out by NMR (SNIF-NMR) for the side chains and the overall content by Mass Spectrometry (MSIR). The overall contents in ¹³C measured by MSIR are generally equal to -28.5 ‰ with a typical variation of the order of 2 ‰ and the isotopic contents of ¹³C of the alkylated or
15 functional side chains are measured by NMR. According to the synthesis process and the origin of the primary material of the side chains, the values δ ¹³C can vary between -5 and -100 ‰ and thus offer an important characterization potential.

20 Nitrated molecules of synthetic origin have ¹³C and ¹⁵N values, measured by MSIR, which are relatively low and equal respectively to -30 ‰ (1.5) and -20 ‰ (10) but, in this latter case, the cyclization reactions of pyrazoles and xanthenes lead to substantial impoverishment in heavy

isotopes. At this level, it can be considered that the values of $\delta^{15}\text{N}$ of the CN group or of the CONH_2 group reflect those of the primary materials because the introduction into the 1H-pyrazole pattern takes place without significant isotopic fractionation. The content in ^{15}N of the NH_2 group is all the lower relative to that of the primary material, the lower is the yield of the reaction.

Commercial chlorosulfonic acids are generally made from sulfuric acid whose ^{34}S content can vary between -25 and +25 ‰ according to the origin of the primary material (native sulfur, pyrites) and of the process of production. However, once synthesized, the $-\text{SO}_2-$ group is an excellent natural tracer and the content in ^{34}S is determined by MSIR.

Finally, it is interesting to note that the isotopic mapping of citric acid is very well defined and that the origin of the sildenafil citrate can be precisely determined by consideration of the isotopic distribution in the citrate fragment. Thus, the content of ^2H measured by NMR varies between -40 and -80 ‰ for biotechnological citric acids but the values $\delta^{13}\text{C}$ are equal respectively to -11 ‰ (1) or -25 ‰ (1) accordingly as the primary material is constituted by a C34 or C3 sugar. The natural citric

acids extracted from fruits such as citrus, pineapple or red fruits have $\delta^2\text{H}$ values that are very near to 0 ‰ (25).

The range of variation which we have shown proves the feasibility of the process for production of a medication or active product. A great possibility of choice of isotopic values of one or several fragments is offered to the producing company desiring to carry out a "natural marking" of its product.

d) Characterization of the different reaction steps by establishment of an isotopic fractionation profile:

▪ Step: level -4 \rightarrow level -3

No modification of the ^2H and ^{13}C contents of the benzene ring is achieved and, in the same way, the $\delta^{18}\text{O}$ value of the ethoxy group must not vary. The most significant variation is in the NH_2 function of P(-4a) which is subject to isotopic fractionation $^{15}\text{N}/^{14}\text{N}$ proportional to the kinetic effect α of the formation reaction of the amide bond and the corresponding fractionation is measured by MSIR.

It is to be noted however that the primary material P(-4b), 2-ethoxy benzoic acid, can be naturally and specifically marked without the addition of enriched molecules, in the following manner:

The $\text{O}-\text{C}_2\text{H}_5$ group is naturally marked with ^2H , ^{13}C or ^{18}O from suitably chosen ethanol molecules. An ethanol

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synthesis has ^2H values equal respectively to $\delta 100$ and $\delta 160$
□ at the two CH_3 and CH_2 sites with ^{13}C contents of the order
of $\delta 28$ to $\delta 31$ □ and $\delta 18$ contents equal to $\delta 5-10$ □.
Moreover, a natural ethanol could have ^2H , ^{13}C , or ^{18}O
5 contents equal respectively to $\delta 200$ and $\delta 400$ □ (^2H), -11 □
(^{13}C) and $+7/+10$ (^{18}O). These two types of commercially
available ethoxy groups without enriched addition, are
easily introduced into the o-hydroxybenzoic acid molecule
by means of conventional reactions to form the primary
10 material P(-4b). The isotopic characteristics of this
primary material, which become a typical fragment as
described above, are present in the final molecule of
sildenafil citrate.

▪ Step: level -3 \rightarrow level -2

15 In the course of this step, there can be observed by MSIR
characteristic variations of the $\delta^{15}\text{N}$ contents of the
nitrogen atoms of the pyrimidinone ring

The $\delta^2\text{H}$ and $\delta^{18}\text{O}$ values of the NH and C=O sites are not
usable because they depend on chemical exchanges with the
20 medium.

▪ Step: level -2 \rightarrow level -1

In the course of this reaction step, the benzene ring is
sulfonated by means of a reaction of the electrophilic
substitution type at low temperature. The ^{34}S content,

measured by MSIR, can be very slightly modified, but this modification is the less as the sulfonation yield is higher. No modification is expected for the other isotopomers of P(-1a).

5 ▪ Step: level -1 --→ level 0

The attachment of the piperazine ring of (P-1b) to the sulfonyl group of P(-1a) can give rise to a slight decrease in ^{15}N of the piperazine fragment fixed to the sildanefil sulfate. This decrease, which is measured by MSIR, can if

10 desired be characterized in the cleavage product of sildanefil citrate. The other isotopic contents are not changed in the course of this step.

CLAIMS

1. Process for the analysis of a sample of a complex molecule relative to a reference batch of the same complex molecule so as particularly to determine their degree of similarity and/or the nature of their process of production,

characterized in that the complex molecule is cleaved into at least two molecular sub-entities, in that, if necessary, at least one of the cleavage products is cleaved into at least two new molecular sub-entities and in that this cleavage operation is repeated on at least a portion of the cleavage products until analyzable and isolable molecular sub-entities are obtained, in that there is determined, as a function of the atomic sites of the cleavage products in question, by generally chemical cleavage reactions, the isotope or isotopes to be studied, in that there is established, for at least a portion of the cleavage products, their isotopic profile and in that the isotopic profile of the cleavage products is compared to the isotopic profile of primary materials already cataloged and taking part in the synthesis process of the reference complex molecule and/or in the isotopic profile of the cleavage products of the reference complex molecule subjected to the same cleavage reactions.

2. Process according to claim 1,

characterized in that, starting from a selected isotope or isotopes, there is established the isotopic profile of at least a portion of the cleavage products at least by nuclear magnetic resonance NMR for the measurement of the specific positional isotopic content and if desired by mass spectrometry, of the isotopic ratios for measuring the overall isotopic content.

3. Process according to one of claims 1 and 2,

characterized in that, during production of the complex reference molecule before being subjected to the same cleavage reactions as the complex molecule to be analyzed, there is selected at least one primary material and/or an intermediate product and/or material synthesis conditions to give to at least one of the cleavage products of the reference complex molecule a unique characteristic detectable during analysis without enrichment by isotopic marking and/or the addition of exogenous elements.

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Gérard [FR/FR]; 21, rue Thomas Maisonneuve, F-44000
Nantes (FR). MARTIN, Gilles [FR/DE]; Bücher, Haupt-
strasse 25, D-90427 Nürnberg (DE).

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(71) Déposant (*pour tous les États désignés sauf US*): EU-
ROFINS SCIENTIFIC [FR/FR]; Site de la Géraudière,
Rue Pierre Adolphe Bobierre, F-44301 Nantes Cedex
(FR).

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(72) Inventeurs; et

(75) Inventeurs/Déposants (*pour US seulement*): MARTIN,

(54) Title: METHOD FOR ANALYSING A SAMPLE OF A COMPLEX MOLECULE RELATIVELY TO A REFERENCE
BATCH OF THE SAME COMPLEX MOLECULE

(54) Titre: PROCEDE D'ANALYSE D'UN ECHANTILLON D'UNE MOLECULE COMPLEXE PAR RAPPORT A UN LOT DE
LA MEME MOLECULE COMPLEXE DE REFERENCE

(57) Abstract: The invention concerns a method for analysing a sample of a complex molecule relatively to a reference batch of the same complex molecule. Said method is characterised in that it consists in breaking up the complex molecule into at least two molecular sub-entities; in determining, on the basis of the atomic sites of said products of the breakup involved in the breakup reactions, the isotope(s) to be analysed; and in establishing, for at least part of the breakup products, their isotopic profile; and in comparing the isotopic profile of the products of the breakup with the isotopic profile of the raw material(s) previously indexed and/or with the isotopic profile of the reference complex molecule subjected to the same breakup reactions. The invention is useful for detecting counterfeiting in manufacturing processes.

(57) Abrégé: L'invention concerne un procédé d'analyse d'un échantillon d'une molécule complexe par rapport à un lot de la même molécule complexe de référence. Ce procédé est caractérisé en ce qu'on scinde la molécule complexe en au moins deux sous-entités moléculaires, en ce qu'on détermine, en fonction des sites atomiques des produits de scission concernés par les réactions de scission, le ou les isotopes à étudier, en ce qu'on établit, pour au moins une partie des produits de scission, leur profil isotopique et en ce qu'on compare le profil isotopique des produits de scission au profil isotopique de matière(s) première(s) déjà répertoriée(s) et/ou au profil isotopique de produits de scission de la molécule complexe de référence soumise aux mêmes réactions de scission. Application: détection de contrefaçons de procédés de fabrication.

WO 00/79569 A2

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: _____

the specification of which: (check one)

REGULAR OR DESIGN APPLICATION

- ☐ is attached hereto.
- ☐ was filed on _____ as application Serial No. _____ and was amended on _____ (if applicable).

PCT FILED APPLICATION ENTERING NATIONAL STAGE

- ☒ was described and claimed in International application No. PCT/FR00/01712 filed on June 21, 2000 and as amended on _____ (if any).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

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I hereby claim foreign priority benefits under 35 USC 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN APPLICATION(S)

Country	Application Number	Date of Filing (day, month, year)	Priority Claimed
France	99/07943	22-06-1999	Yes

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional patent application(s) listed below:

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Filing Date

(Status—patented, pending, abandoned)

(Complete this part only if this is a continuing application.)

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(Application No.)

(Filing Date)

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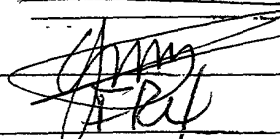
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c/o YOUNG & THOMPSON,
Second Floor,
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Address all telephone calls to Young & Thompson at 703/521-2297. Telefax: 703/685-0573.

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Full name of sole or first inventor: Gerard MARTIN

Inventor's signature: 

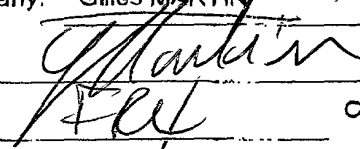
Date: 12/01/2002

Residence: Nantes, France

Citizenship: France

Post Office Address: 21, rue Thomas Maisonneuve 44000 Nantes, France

Full name of second joint inventor, if any: Gilles MARTIN

Inventor's signature: 

Date: 11/1/2002

Residence: Nurnberg, Allemagne

Citizenship: France

Post Office Address: Bucher, Hauptstrasse 25, 90427 Nurnberg, Allemagne

Full name of third joint inventor, if any: _____

Inventor's signature: _____

Date: _____

Residence: _____

Citizenship: _____

Post Office Address: _____

Full name of fourth joint inventor, if any: _____

Inventor's signature: _____

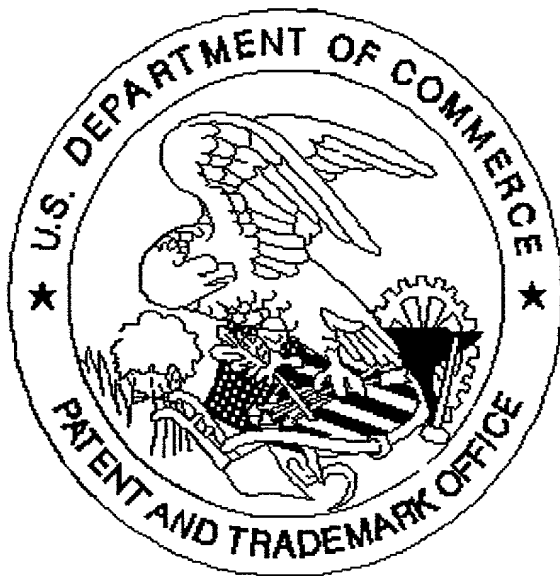
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